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Evidence for central venous pressure resetting during initial exposure to microgravity

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Convertino, Victor A., David A. Ludwig, James J. Elliott, and Charles E. Wade. Evidence for central venous pressure resetting during initial exposure to microgravity. *Am J Physiol Regulatory Integrative Comp Physiol* 281: R2021–R2028, 2001.—We measured central venous pressure (CVP); plasma volume (PV); urine volume rate (UVR); renal excretion of sodium (UNa); and renal clearances of creatinine, sodium, and osmolality before and after acute volume infusion to test the hypothesis that exposure to microgravity causes resetting of the CVP operating point. Six rhesus monkeys underwent two experimental conditions in a crossover counterbalance design: *1*) continuous exposure to 10° head-down tilt (HDT) and *2*) a control, defined as 16 h/day of 80° head-up tilt and 8 h prone. After 48 h of exposure to either test condition, a 120-min course of continuous infusion of isotonic saline (0.4 $ml \cdot kg^{-1} \cdot min^{-1}$ iv) was administered. Baseline CVP was lower ($P = 0.011$) in HDT (2.3 ± 0.3 mmHg) compared with the control (4.5 ± 1.4 mmHg) condition. After 2 h of saline infusion, CVP was elevated ($P = 0.002$) to a similar magnitude ($P = 0.485$) in HDT (ΔCVP = 2.7 ± 0.8 mmHg) and control (ΔCVP = 2.3 ± 0.8 mmHg) conditions and returned to preinfusion levels 18 h postinfusion in both treatments. PV followed the same pattern as CVP. The response relationships between CVP and UVR and between CVP and UNa shifted to the left with HDT. The restoration of CVP and PV to lower preinfusion levels after volume loading in HDT compared with control supports the notion that lower CVP during HDT may reflect a new operating point about which vascular volume is regulated. These results may explain the ineffective fluid intake procedures currently employed to treat patients and astronauts.

set point; hypovolemia; diuresis; renal function

PLASMA VOLUME (PV) and central venous pressure (CVP) are reduced within the initial 24–48 h of exposure to actual and ground-based analogs of microgravity (1, 6, 7, 12, 13, 18). Reductions in vascular volume and CVP might, in part, explain the inability of astronauts to maintain cardiac filling volumes and orthostatic tolerance on reentry from spaceflight (3, 15). Consequently, in the space shuttle program, National Aeronautics and Space Administration (NASA) flight surgeons implemented a fluid-loading countermeasure in which astronauts were instructed to ingest eight 1-g salt tablets with 960 ml of water ~2 h before reentry from space (3). Although preliminary results were encouraging with space missions of 54 to 145 h (~2–6 days) duration (3), this fluid-loading regimen appeared to have limited impact on orthostatic tolerance after space missions longer than 7 days in duration (2, 19). An inability of fluid loading to ameliorate orthostatic compromise after longer spaceflights was not surprising in light of the observation that PV could not be returned to ambulatory levels in subjects who underwent exposure to a ground-based analog of microgravity and followed the same fluid-loading regimen as the astronauts (18).

One possible explanation for the inability of fluid loading to protect against orthostatic compromise after space missions is that failure to restore PV may represent a "resetting" of blood volume regulation to a lower operating point (6, 7, 9). Such a notion as resetting is supported by the observation that the diuresis in human subjects induced by acute saline infusion during exposure to head-down tilt (HDT) for 6 days was similar to the diuresis measured before HDT when the subjects had a larger PV (9). Unfortunately, neither PV nor CVP were measured to determine whether they were elevated and then returned to their preinfusion levels. In a subsequent experiment (7), HDT was associated with a shift in the relationship between CVP (stimulus) and forearm vascular resistance (response) to a lower CVP operating range, also supporting the possibility that the operating point for blood volume

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regulation may have been reset to a lower range. However, vascular volume was lowered by HDT in the latter investigation, and, without a volume load designed to increase CVP and urine output, the investigators could not determine whether the shift in the CVP-vascular resistance relationship represented a resetting of the operating point or simply a reduced vascular volume.

In previous investigations, our laboratory (8, 13) developed a ground-based analog of microgravity (10° HDT) in an invasively instrumented rhesus monkey model and demonstrated a reduction in CVP that was in agreement with human data obtained from both spaceflight (1, 12) and ground-based (7, 18) experiments. In the present study, we hypothesized that the reduction in PV and CVP due to HDT represents a resetting of the operating range for regulation of blood volume. To test this hypothesis, we conducted an investigation in which we administered an acute volume load (stimulus) and measured responses in CVP, PV, and renal functions. If our hypothesis proved true, we would expect the elevation in PV and CVP induced by saline infusion to diminish and PV and CVP to return to preinfusion levels in both HDT and upright control conditions despite lower vascular volume during HDT. In contrast to previous experiments, our approach was novel in that it provided information on alterations in CVP and vascular volume during HDT that are necessary for interpretation of a proposed operating point resetting hypothesis.

METHODS

Subjects. The animals involved were procured, maintained, and used in accordance with the Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources-National Research Council, and all experimental procedures and protocols were reviewed and approved by the Institutional Animal Care and Use Committee. The Veterinary Sciences Research Laboratory where the experiments were conducted has been fully accredited by the American Association for Accreditation of Laboratory Animal Care since 1967.

Six mature male rhesus monkeys (*Macaca mulatta*) averaging 4.5–8.0 kg in weight were selected as subjects for this study. The monkeys received 2 mo of tilt table adaptation training before the experiments. This training involved three phases consisting of *1*) preliminary caretaker handling, restraint jacket fitting, and light ketamine sedation; *2*) acute restraint jacket and tilt table acclimation training (~2 h); and *3*) increased restraint jacket and tilt table adaptation training (≤24 h).

After verification that the monkeys were able to adapt to the tilt table during all phases of training, they were chronically instrumented with an indwelling jugular catheter that was advanced to terminate in the anterior vena cava just outside the right atrium. This catheter provided an access site for acute insertion of a single-tip 3 French micromanometer (Millar Instruments, Houston, TX) for measurement of CVP and infusion of saline. Subjects were given at least 1 wk of postoperative recovery before the start of the test protocol.

Experimental design. The use of the rhesus monkey in the 10° HDT position was chosen because actual changes in cardiovascular and renal responses reported in humans during exposure to spaceflight have been closely simulated in this ground-based animal model (5, 8, 13). A standard two-treatment crossover design was used, with each monkey receiving both 10° HDT and upright/prone control conditions. The treatment order was randomized but counterbalanced so that three monkeys received HDT followed by the control condition and three monkeys received the control condition followed by HDT. Each treatment period lasted 96 h (4 days). The monkeys were kept unrestrained in their cages for a period of 9 days between treatment periods (i.e., crossover interval). The temperature and humidity of the laboratory and cage rooms were maintained at 24 ± 1°C and ~40%, respectively. An additional "time" (repeated measures) effect independent of the posture treatments was introduced because some of the dependent variables under study were measured over various time courses.

Measurement techniques. Test subjects were trained and tested on custom-designed and fabricated HDT tables that were positioned at one of three settings: 10° HDT, 0° prone, or 80° head-up tilt, as previously described (13) (Fig. 1). Animals were continuously monitored throughout the exper-

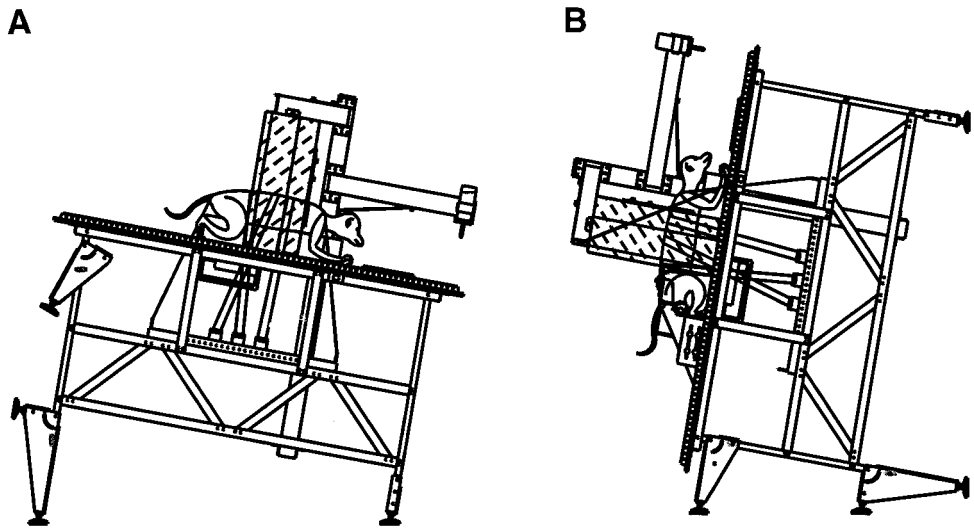

Fig. 1. Illustration of experimental apparatus for nonhuman primate microgravity model with head-down tilt (HDT) condition (*A*) and head-up tilt (HUT) control condition.

imental procedures. The control condition consisted of 16 h of 80° head-up tilt (lights on 0700–2300) and 8 h of 0° prone to provide a sleeping posture (lights off 2300–0700). The HDT treatment condition consisted of continuous exposure (i.e., 24 h/day) to 10° HDT. During each experimental condition, water and food were provided ad libitum and intake amounts were recorded. A standard monkey diet biscuit (LabDiet) of ~3.5 g with a caloric density equal to 4 kcal/g (69% carbohydrate, 13% fat, 18% protein) was used as the primary food source.

Isotonic saline infusion test. From ~0900 to 1200 on *day 3* of restraint, each animal was lightly sedated with a steady-state infusion of ketamine ($0.15 \cdot mg \cdot kg^{-1} \cdot min^{-1}$) given via the atrial access catheter and was placed in the prone (0°) posture for the isotonic saline infusion experiment. We chose to standardize the position of the animal in the prone posture during the saline infusion tests in both control and HDT conditions so that we could eliminate posture as a contributing factor to physiological responses during infusion. From ~0900 to 0930, we placed a temporary catheter in the saphenous vein for withdrawal of serial blood samples, inserted the Millar pressure transducer into the indwelling jugular catheter, and inserted a 5 French Foley urinary catheter for collection and measurement of urine volume. At ~0930, the subjects' bladders were evacuated with a 25-ml syringe without flush. At ~1000, after a minimum time of 30 min between the last instrumentation procedure and bladder evacuation, the saline infusion experiment was initiated (*time 0*) with a continuous intravenous infusion of 0.9% saline ($0.4\ ml \cdot kg^{-1} \cdot min^{-1}$) through the atrial access catheter. The saline infusion was continued for 2 h (1000–1200) during which time the subjects' bladders were evacuated at *times 0, 30, 60, 90,* and *120* min. Measurements of CVP were also made at *times 0, 30, 60, 90,* and *120* min and repeated 18 h after the cessation of saline infusion. CVP was measured as an analog signal from an Ectron amplifier (model 428) and displayed on a Gould four-channel physiological monitor as an analog waveform and converted to a digital output. The digital CVP output was manually recorded as a mean pressure. Blood samples (2 ml each) were taken at 0, 60, and 120 min during the 2-h experimental period to measure plasma concentrations of sodium, potassium, osmolality, and creatinine and to calculate renal clearances of these solutes. Blood samples were also used to measure venous hematocrit. In addition, heart rate and systolic, diastolic, and mean arterial blood pressures (noninvasive automated sphygmomanometry from the right arm) were measured every 30 min.

Responses in renal functions. Plasma and urine samples were analyzed for concentrations of sodium and creatinine with an ion-sensitive electrode system (Nova 16). Plasma and urine osmolality were measured by freezing-point depression (model 3D3 osmometer; Advanced Instruments). Urine volume rate (UVR) was calculated as the volume of urine collected divided by the time duration of the collection. Renal sodium excretion (UNa) was calculated as the volume of urine collected multiplied by the corresponding urine sodium concentration. Sodium (CNa) and osmotic (Cosm) clearances were calculated as the rate of sodium or osmotic excretion divided by the mean plasma concentrations. Glomerular filtration rate was estimated from the clearance rate of creatinine (Ccr; creatinine excretion rate divided by plasma creatinine concentration).

PV measurement. PV was measured before the saline infusion test with a modified dilution technique that used sterile solutions of Evans blue dye contained in 10-ml ampules (New World Trading, DeBary, FL). A preinjection control blood sample was drawn, followed by an intravenous injection of ~5 mg of dye diluted with isotonic saline solution (1.5 ml). One milliliter of plasma from a 10-min postinjection blood sample was passed through a wood-cellulose powder (Solka Floc SW-40A) chromatographic column so that the dye could be absorbed. The absorbed dye was eluted from the column with a 1:1 water-acetone solution (pH 7.0) and collected in a 10-ml volumetric flask. The postinjection solution was compared with 1-ml samples from a preinjection time (0 control) and a standard dye solution (1:50 dilution with distilled water), and all samples were read at 615 nm with a spectrophotometer. With the use of these procedures in our laboratory, the test-retest correlation coefficient for PV was 0.969 (n = 12 samples), and the average changes (Δ) were 82 (average $\%\Delta$= 1.5%; n = 17 samples), 75 (average $\%\Delta$ = 1.5%; n = 19 samples), and 56 (average $\%\Delta$ = 1.1%; n = 23 samples) ml when measurements were determined 4, 8, and 15 days apart, respectively (10). The percent change in PV ($\%\Delta$PV) was calculated from changes in venous hematocrit from samples that were collected before and at 60 and 120 min and 18 h postinfusion (17). Absolute PV after infusion was calculated as the product of $\%\Delta$PV and baseline PV.

Statistical methods. A standard two-treatment (control, HDT) × three time period (0, 60, and 120 min) within-subjects repeated-measures ANOVA was used to test if differences in CVP, PV, UVR, renal functions, and hemodynamic responses measured over time periods during saline infusion were the same for each treatment condition (i.e., if treatment profiles over time were parallel). The same statistical model was used to evaluate changes in CVP and PV over the 18-h time period after saline infusion. The only difference between the postinfusion CVP and PV time-course model and the model used for the pre- to postsaline infusion was the existence of six rather than four time levels. P values were calculated for each independent effect and reflect the probability of observing the measured effect, or one larger, given only random error. Separate error terms were generated for each effect in the statistical model. All statistical tests were based on six animals. Error bars presented in the figures reflect simple SEs around means but do not reflect variations specific to the experimental design or the variability associated with the statistical tests.

RESULTS

Dietary intake. Average daily (24 h) fluid intake during HDT (400 ± 137 ml) was not statistically different (t = 0.58, P = 0.595) from that of animals in the control condition (421 ± 171 ml). Daily calorie and sodium intakes were 126 ± 19 kcal and 105 ± 17 mg, respectively, in the control condition compared with 152 ± 25 kcal and 107 ± 22 mg during HDT (t = 0.566, P = 0.596).

The time course of CVP and PV by treatment condition is presented in Fig. 2. As expected, baseline PV was reduced by 12% (F = 26.27, P = 0.004) during HDT (305 ± 20 ml) compared with control (345 ± 16 ml) conditions, and baseline CVP was lower (F = 7.22, P = 0.011) in HDT (2.3 ± 0.3 mmHg) compared with the control (4.5 ± 1.4 mmHg) condition. PV and CVP demonstrated an overall main effect (increase) during saline infusion [$F(1,5)$ = 11.65, P = 0.002]. The elevation in CVP during 2 h of saline infusion was similar in magnitude (F = 0.778, P = 0.485) in HDT (ΔCVP = 2.7 ± 0.8 mmHg) and control (ΔCVP = 2.3 ± 0.8 mmHg) conditions. At 18 h postinfusion, control and

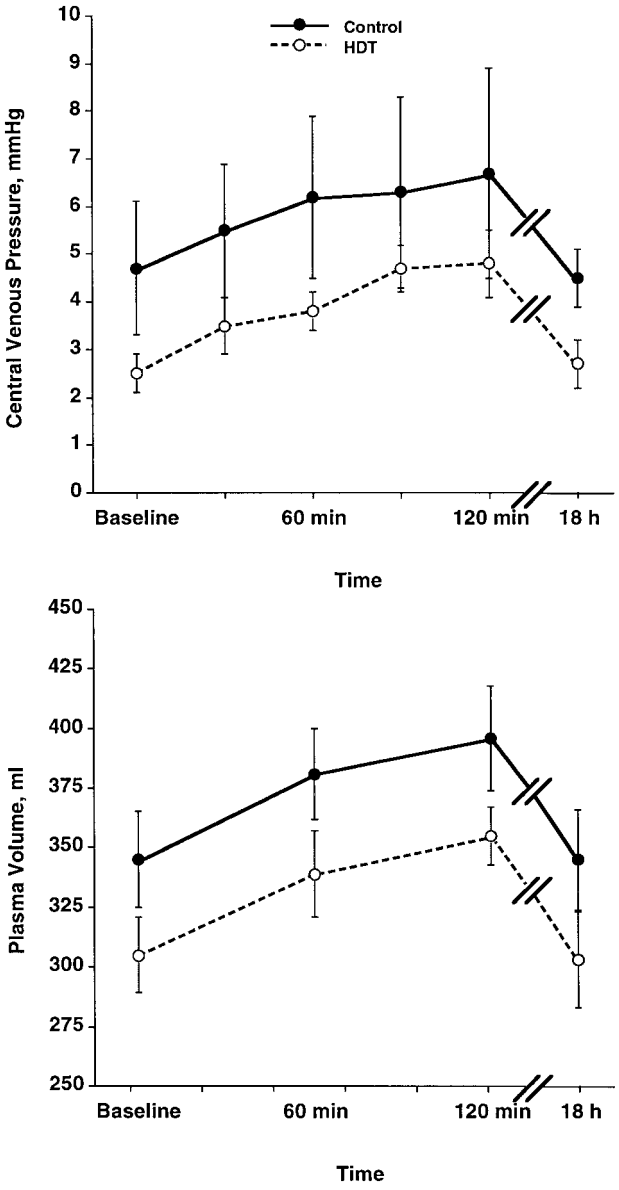

Fig. 2. Responses of central venous pressure and plasma volume before (baseline), at 60 and 120 min during and 18 h after the termination (double slanted lines) of saline infusion for control and HDT conditions. Values are means ± SE.

HDT CVP values were virtually identical to preinfusion baseline values for control (4.5 vs. 4.3 mmHg) and HDT (2.3 vs. 2.7 mmHg) conditions. Similarly, the expanded PV during 2 h of saline infusion was similar in magnitude (F = 0.02, $P = 0.884$) in HDT ($\Delta PV = 51 \pm 4$ ml) and control ($\Delta PV = 49 \pm 10$ ml) conditions and returned to preinfusion levels by 18 h postinfusion (Fig. 2).

Mean values ± SE for UVR, Ccr, CNa, and Cosm at baseline and during saline infusion are presented by treatment condition in Fig. 3. Ccr was unaltered by saline infusion [$F(1,5) = 0.51$, $P = 0.614$] or HDT [$F(1,5) = 0.42$, $P = 0.827$]. As expected, UVR, CNa, and Cosm demonstrated an overall main effect (increase) due to saline infusion [$F(1,5) = 7.88$, $P = 0.009$]. However, we could not distinguish a statistical difference between HDT and control conditions for UVR, CNa, and Cosm during saline infusion [$F(1,5) = 0.45$, $P = 0.531$].

The mean stimulus-response relationships between CVP and UVR and between CVP and UNa are presented by treatment condition in Fig. 4. HDT caused a parallel shift to the left in both relationships.

Hemodynamic responses. Mean heart rate and arterial blood pressures are presented by treatment condition and time before and during saline infusion in Fig. 5. Neither heart rate nor the blood pressures showed statistically discernible effects of treatment [$F(1,5) = 0.60$, $P = 0.474$], time [$F(4,20) = 1.55$, $P = 0.227$], or their subsequent interaction [$F(4,20) = 0.62$, $P = 0.656$].

DISCUSSION

In the present study, we verified that our model of microgravity reduced CVP in a manner similar to that reported in other spaceflight and ground-based experiments (1, 6, 7, 12, 13, 18). We hypothesized that this reduction in PV and CVP as a result of HDT represented a resetting of the operating point for blood volume regulation to a lower operating range. If the operating point for CVP were not altered and lower vascular volume were driving CVP, then one might expect that restoration of vascular volume after the termination of fluid loading in the HDT treatment would settle at the same CVP as that in the control condition. In contrast to this possibility, CVP increased as a result of saline infusion in both control and HDT conditions but eventually returned to its preinfusion level despite a lower PV in HDT. These results support our hypothesis that microgravity, as simulated by HDT, lowered the operating point around which blood volume is regulated.

The notion that microgravity reduces the operating point for blood volume regulation was initially supported by the results of a ground-based experiment in which subjects who received intravenous infusion of isotonic saline solution (22 ml/kg body wt) showed similar urine outputs before, compared with their sixth day of, exposure to HDT (12). Unfortunately, interpretation of similar urine outputs during equal saline infusion was limited because the investigators failed to conduct simultaneous measures of either PV or CVP. The observation that our monkeys demonstrated similar urine outputs and renal responses to equal saline infusion are consistent with previous findings (12) and extend these results by demonstrating that both PV and CVP increase equally and return to their initial preinfusion level in a similar fashion. Our experiments provide new insight that the equal renal response to equal volume loading at a lower operating range of CVP represents resetting (Fig. 4).

The hypothesis that exposure to microgravity could induce a resetting of the operating point for blood volume regulation was also advanced by the previous observation that exposure of human subjects to 7 days

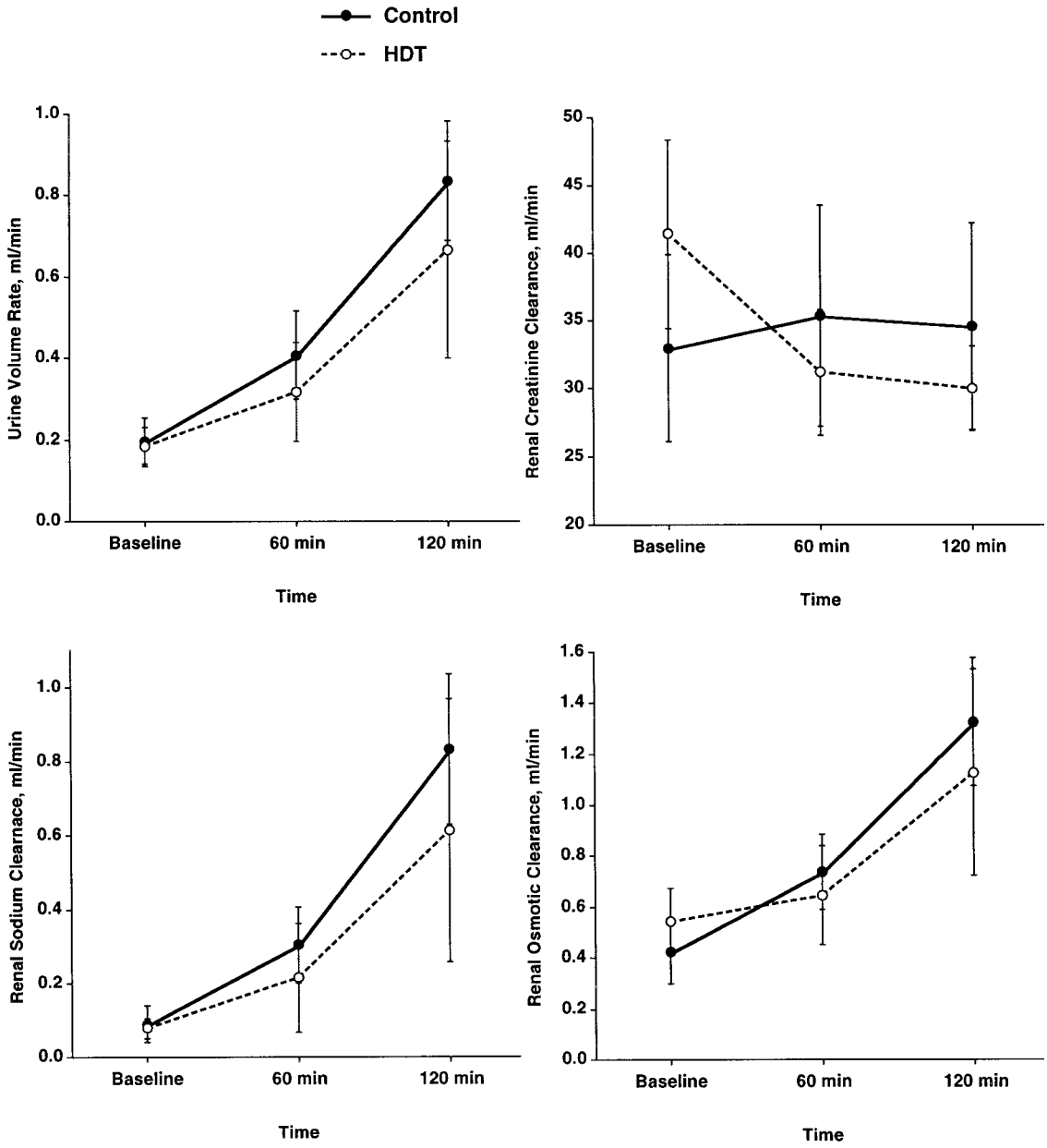

Fig. 3. Responses of urine volume and renal creatinine, sodium, and osmotic clearances before (baseline) and at 60 and 120 min during saline infusion for control and HDT conditions. Values are means ± SE.

of HDT caused the low-pressure baroreflex stimulus-response relationship to shift to the left so that the response for peripheral vascular resistance occurred in a lower range of CVPs (7). Although the shift of this stimulus-response relationship provided supporting evidence of a resetting for the operational range of CVP, it was not possible to interpret the meaning of this alteration with regard to control of PV, because there was no manipulation of vascular volume (stimulus) with subsequent measurement of urine output (response). Consistent with this earlier observation of shifts in the low-pressure baroreflex stimulus-response relationship (7), we observed similar responses of urine output and renal functions to equal saline infusion with a lower baseline and operational range of CVP in the present investigation. Our results extend previous findings by demonstrating that equally elevated urine output and UNa at lower CVP observed in our monkeys after adaptation to simulated microgravity can be primarily explained by a resetting to a lower operational range represented by a parallel shift in the CVP-UVR and CVP-UNa stimulus-response relationships (Fig. 4).

Under our experimental conditions, equal volume rates of saline administration resulted in similar elevations in CVP, PV, and renal clearances of sodium and osmotic solutes without affecting creatinine clearance or hemodynamic responses for both HDT and control experimental conditions. Although we did not measure hormones associated with regulation of vas-

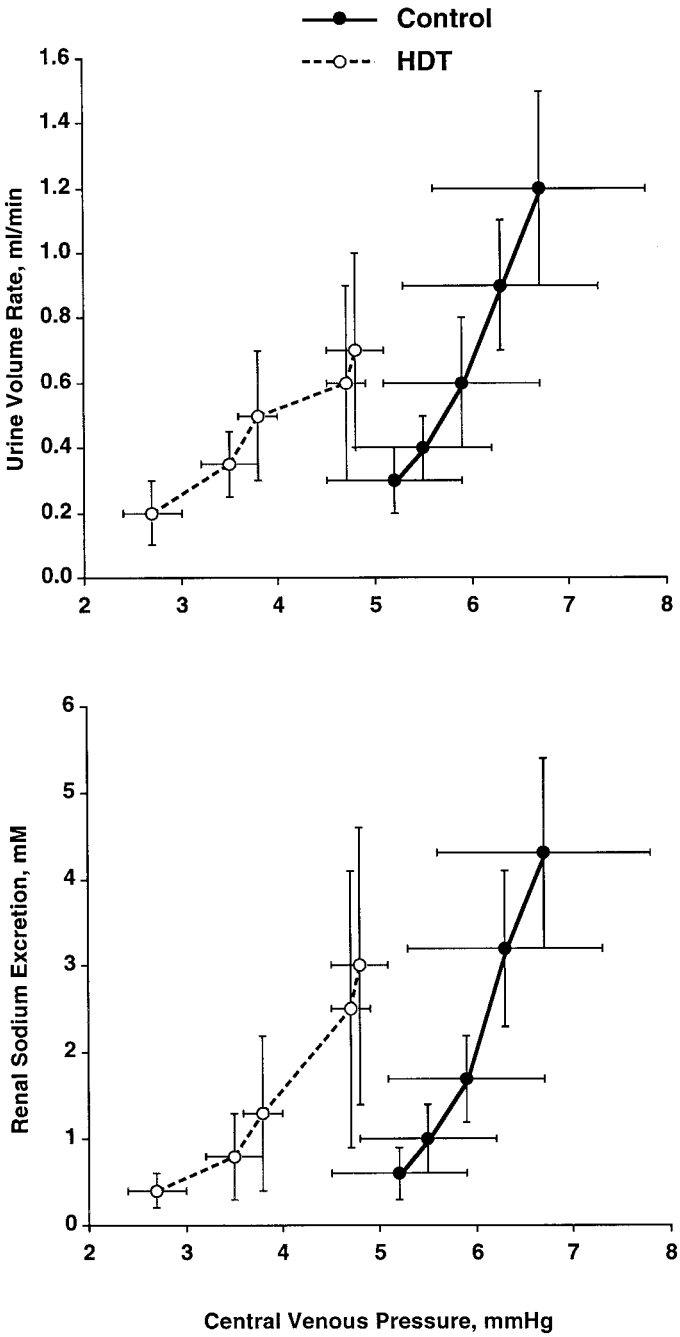

Fig. 4. Relationships between central venous pressure (*x*-axes) and urine volume rate (*top*) and between central venous pressure and renal sodium excretion (*bottom*) before and after volume loading (saline infusion) for control and HDT conditions. Values are means ± SE.

cular volume in the present investigation, we have reported similar levels of plasma renin activity, vasopressin, atrial natriuretic hormone, and cortisol after similar elevations in PV and CVP with Dextran infusion with the same HDT and control conditions (8). Therefore, it is unlikely that our interpretation that a surrogate model of microgravity caused resetting of the operational point for blood volume regulation was influenced by hemodynamic factors or renal responses to hormones associated with regulation of body sodium and fluid volume.

As with any investigation, there were limitations to our experimental approach. We specifically chose the use of urinary catheterization as the most accurate collection of urine volume because of the ability to evacuate the bladder at specific time intervals. Our approach of placing a urinary catheter, peripheral venous blood sampling line, and blood pressure cuff on our monkeys necessitated sedation. Therefore, appropriate time control experiments were not possible. Without a set of time control experiments, we cannot dismiss the possibility that sedation, as well as other experimental manipulations, may have contributed to the diuresis and natriuresis. We are unaware of investigations in which the sedative and experimental ma-

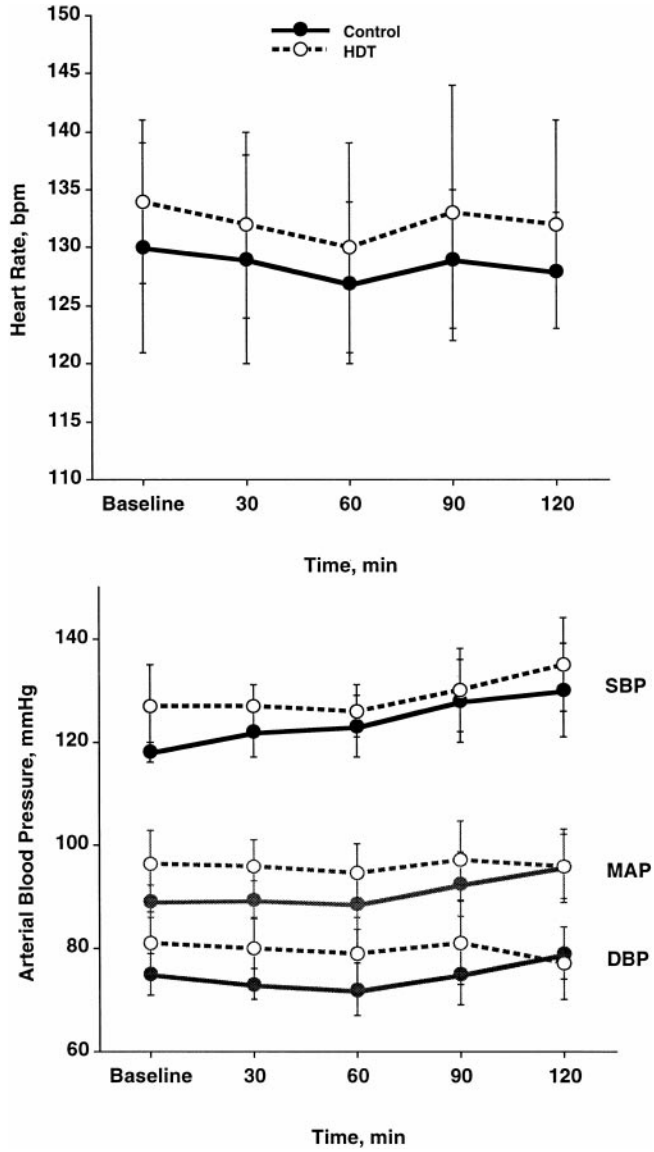

Fig. 5. Responses of systolic (SBP), diastolic (DBP), and mean arterial (MAP) blood pressures and heart rate at baseline and during 2 h of intravenous infusion of saline during HDT and the control treatment. Values are means ± SE. bpm, Beats/min.

nipulations used in the present study have affected renal functions. However, compared with conscious control values, ketamine did not alter arterial blood pressure (4, 14), cardiac output (14), peripheral vascular resistance (14), baroreflex functions (14), and numerous endocrine responses (4) in monkeys. Furthermore, saline loads similar to the one given in the present experiment and designed to expand PV caused pronounced diuresis and natriuresis in conscious humans (9, 16). It therefore seems most likely that the diuresis and natriuresis observed in the present study resulted from saline infusion rather than sedation or other experimental manipulations. More importantly, the stimulus for diuresis and natriuresis should have no impact on our interpretation because our experimental design assured that the same animals were exposed to the same experimental manipulations (including sedation and other experimental procedures) under both HDT and control conditions. Therefore, we should expect the elevation in CVP during infusion to return to its preinfusion levels in both HDT and upright control conditions despite lower vascular volume during HDT if CVP resetting occurred.

In contrast to our results, attenuated urine output during exposure to simulated or actual microgravity has been reported. In a previous investigation (8) that used the same model as that of the present investigation, we reported that urine volume during Dextran infusion was 67% lower during HDT compared with the control condition. Attenuated urine output in the former study may be partly explained by a greater hyperoncotic and hyperosmotic effect of Dextran on water filtration from renal tubules to tubular capillaries, consequently reducing urine formation in a hypovolemic state of HDT. Norsk et al. (16) reported a 55% attenuation in average urine output during saline infusion in astronauts during spaceflight compared with the supine posture on earth. However, it is difficult to compare and interpret the differences between the spaceflight data and the results of the present investigation because PV and CVP were not measured, and there was no control group (condition) during the infusion experiments in spaceflight. Therefore, when experimental protocols and procedures can be carefully controlled and compared with similar methodologies, the results of the present investigation are in agreement with human ground-based experimental results showing that urine output during equal saline infusion remains similar between microgravity and normogravity conditions as long as the elevation in CVP and PV are experimentally controlled.

Despite the evidence from our present investigation, the physiological mechanism(s) underlying the apparent longitudinal resetting of the operational point for blood volume regulation during microgravity is unexplained. Numerous brain nuclei and neural pathways have been identified as integrators for processing information from systemic receptors for controlling plasma and blood volume. One possible hypothesis is that extended exposure to microgravity induces long-term adaptation of this "visceral neuroaxis" so that the same level of CVP (input) from low-pressure receptors produces a greater renal excretion of water and electrolytes (output), thus changing the processing function of the central nervous system integrator (11). This hypothesis will remain speculative until future experiments are designed to investigate the neural plasticity of peripheral and central nervous system mechanisms associated with blood volume regulation.

Perspectives

Because hypovolemia induced by prolonged exposure to low gravity, i.e., supine posture or spaceflight, is related to reduced physical working capacity and orthostatic tolerance, restoration of blood volume has clinical implications for the recovery of normal physiological function in bedridden patients and astronauts. The implication that current oral fluid-loading countermeasures can successfully restore PV is based on an assumption that the relationship between the operational point for feedback regulation of vascular volume has remained intact. Contrary to this notion, the return of PV and CVP to a lower level after volume expansion by saline infusion in the present investigation provides compelling evidence that the chronic reduction in PV and CVP during bedrest or spaceflight reflects a change to a lower operating point for blood volume regulation. Consequently, the elevation in CVP resulting from oral fluid loading initiates a feedback diuresis and natriuresis that serves to return blood volume to its contracted state. Therefore, the attempt to use increased oral fluid intake or intravenous saline infusion as a treatment for hypovolemia will only prove minimally effective without an additional manipulation designed to restore the operating point for blood volume regulation to premicrogravity exposure levels.

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